Lecture 14 by Dr.Alaa F. Alwan

NORMAL HEMOSTATIC MECHANISMS

The hemostatic system consists of blood vessels, platelets, and the plasma coagulation system including the fibrinolytic factors and their inhibitors. When a blood vessel is injured, three mechanisms operate locally at the site of injury to control bleeding: (1) vessel wall contraction, (2) platelet adhesion and aggregation (platelet plug formation), and (3) plasmatic coagulation to form a fibrin clot. All three mechanisms are essential for normal hemostasis. Abnormal bleeding usually results from defects in one or more of these three mechanisms.

CLINICAL EVALUATION

1.history

2.Physical Examination

The usual lesions encountered are spontaneous petechiae and ecchymoses, which result from a breakdown of the anatomic and physiological integrity of small vessel walls. Petechiae are pinpoint to small areas of skin bleeding, which characteristically appear as crops of lesions in dependent portions of the microvasculature. Larger accumulations of skin lesions are usually called ecchymoses. It is often difficult to differentiate petechiae secondary to a platelet disorder from purpura caused by a defect of the blood vessel wall. The latter can only be proven by the absence of defects in number and function of platelets. Gastrointestinal and genitourinary bleeding may occur spontaneously with abnormalities of platelets and/or coagulation factors. Deep hematomas, areas of palpable skin or soft tissue bleeding, and hemarthroses are most often associated with coagulation factor deficiencies or abnormalities.

Recurrent bleeding for several days usually indicates an underlying bleeding disorder. In women, a careful and thorough history of their menstrual bleeding pattern gives valuable information about the nature of their hemostatic mechanism.

LABORATORY EVALUATION

1. Screening Tests

The platelet count is performed to detect thrombocytopenia, which is defined as a platelet count of less than 150,000.

The bleeding time is defined as the time between the infliction of a small standard cut and the moment the bleeding stops. Bleeding time measures the interactions of the platelets with the vessel wall and the subsequent formation of the primary hemostatic plug. A long bleeding time will be recorded either when the number of platelets is decreased, their function is abnormal, or there is defect of the vessel wall. The bleeding time may also be prolonged when there is a decrease of plasmatic factors, especially the VWF or fibrinogen.

The prothrombin time (PT) may be prolonged because of a deficiency of a factor(s) of the extrinsic coagulation pathway, i.e, factors II, V, VII, X, and/or fibrinogen. A circulating anticoagulant directed against on or more of these factors may also cause a prolongation of the PT. The assay of coagulation factor deficiencies depends on the type of thromboplastin used because each thromboplastin has a different sensitivity. The aPTT may be prolonged in factor 5 , 8, 9 defeciencies.

2. Specific Assays of Coagulation

PLATELET DISORDERS

Production and release of platelets from the bone marrow is controlled by thrombopoietin. Platelets remain in the circulation for approx 7 d. The normal platelet count ranges from 150,000to 400,000

1. Quantitative Disorders of Platelets

Thrombocytopenia, by definition, exists when the platelet count drops below 150,000 although bleeding attributable to thrombocytopenia usually never occurs when the platelet count is above 100,000. Spontaneous bleeding usually occurs with platelet counts less than 20,000. Thrombocytopenia is due either to decreased bone marrow production of platelets or increased destruction and sequestration of the platelets from the circulation, or both.

Thrombocytopenia Due to Decreased Platelet Production

Classification of Thrombocytopenias
Decreased platelet production
• Marrow failure (e.g., aplastic anemia)
• Marrow infiltration (e.g., leukemia, MDS)
• Marrow depression—cytotoxic drugs, radiation
• Selective megakaryocyte depression—drugs, ethanol, viruses, chemicals
• Nutritional deficiency—megaloblastic anemia
• Hereditary causes (rare)—Fanconi syndrome, amegakaryocytic hypoplasia, absent radii syndrome, Wiskott-Aldrich syndrome

Increased platelet destruction
• Immune
– Idiopathic thrombocytopenic purpura
– Other autoimmune states—SLE, CLL, lymphoma
– Drug-induced: heparin, quinidine, quinine, gold, penicilline, cimetidine
– Infectious—HIV, other viruses, malaria
– Posttransfusion purpura
– Neonatal purpura
• Nonimmune
– DIC
– Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome
– Cavernous hemangioma
– Cardiopulmonary bypass
– Hypersplenism

Idiopathic Thrombocytopenic Purpura

ITP occurs in both children and adults. Acute ITP in children is equally common in boys and girls, has its peak incidence at age 2 to 4 yr, and frequently follows a viral infection. More than 80% of these children have a spontaneous remission of their illness in 2 to 4 wk. The peak incidence of ITP in adults is at 20 to 40 yr of age, and the disease is much more common in women than in men (5:1). A number of patients will seek medical attention because of petechiae, purpura, epistaxis, or menorrhagia. In some patients, the hemostatic disorder is unmasked after taking a medication that interferes with platelet function, such as aspirin. However, asymptomatic

thrombocytopenia is discovered in a substantial number of patients during routine blood testing.

Except for clinical signs of bleeding (petechiae), the physical examination is usually unremarkable. Huge enlarged spleen usually suggests a disorder other than ITP. In addition to the platelet count, a white blood cell count and hemoglobin level should be measured in adult patients. ITP has normal white blood cells and hemoglobin, unless chronic bleeding would have caused an iron deficiency anemia. A bone marrow study may be useful to exclude other hematological disorders, especially if a splenectomy is planned. Other tests include those to detect the presence of antinuclear antibodies and rheumatoid factor, thyroid function tests, and serological tests for hepatitis and HIV.

Treatment in Adults

The first issue is to decide whether a patient requires any specific treatment or not. Patients with moderate thrombocytopenia (platelets >50,000) with no history or signs of bleeding do not require therapy and should just be observed. In contrast, patients with clinical signs of bleeding or very low platelet counts, usually less than 20,000, require therapy. Initial therapy consists of corticosteroids (prednisone or prednisolone 1–2 mg/kg/d, which usually will raise the platelet count to safe levels in 70–80 % of the patients within 1 to 2 wk. When the platelet count has risen above 100,000, one can begin to taper the dose of corticosteroids down to 10–15 mg/d. Only a few patients (10–20 %) will have long-lasting remissions following treatment with corticosteroids.

Splenectomy is indicated in patients who become unresponsive to corticosteroids or require prohibitively high doses to maintain the platelet count at an acceptable level. Splenectomy will not only remove the major site of platelet destruction but also a source of platelet autoantibody production. Approximately 70–80% of patients will sustain a long-term remission after splenectomy, and in 60% of patients the platelet count will return to normal. Prior to splenectomy, a vaccination with pneumococcal vaccines is strongly recommended to prevent a life-threatening pneumococcal infection (overwhelming postsplenectomy infection syndrome [OPSI]) that may occur many years after a splenectomy. Splenectomy fails to correct the platelet count in about 25% of adults with ITP. In patients with an initial response to splenectomy followed by a relapse, the possibility of an accessory spleen should be ruled out. Because subsequent treatments pose increased risks to the patients, it should be decided whether treatment in failing patients is absolutely necessary. Treatment options for failing patients include thrombopoitin agonist like romiplostin or eltrombopag, or “pulse-dose” dexamethasone (40 mg/d for days 1–4, every 4 wk), azothioprine, cyclophosphamide, vinca alkaloids, cyclosporine A, and danazole.

INHERITED DISODERS OF BLOOD COAGULATION

Inherited disorders of blood coagulation are due to the lack of synthesis or to the synthesis of a dysfunctional molecule of one and, in rare instances, more than one coagulation factors. Factor VIII and factor IX deficiencies are inherited as a sex-linked trait. Von Willebrand disease (VWD) is inherited in an autosomal dominant manner

Hemophilias A and B

Hemophilia A (factor VIII deficiency) is the most common hereditary disorder of blood coagulation. It is due to the absent or decreased function of coagulation factor VIII, resulting from mutations in the factor VIII gene. The inheritance is sex-linked. Hemophilia A occurs in approx 1 in 10,000 persons. Because the gene for factor VIII is present on the X chromosome, females are usually not affected because they carry only one defective gene. Children of a female carrier have a 50% chance of inheriting the abnormal X chromosome.

The inheritance as well as the clinical features of hemophilia B (factor IX deficiency, Christmas disease) are identical to those of hemophilia A. The incidence is one-fifth of that of hemophilia A. The two disorders can only be distinguished by coagulation factor assays.

CLINICAL PRESENTATION

Excess bleeding is relatively uncommon at birth. The first bleeding problems usually start when a child starts crawling, and this may be from 9 mo to 1 yr of age. Bleeding, however, can occur after surgery, i.e., circumcision. The first signs that parents may notice are large skin bruises. Abnormal and recurrent bleeding can then occur from any part of the body. A dominant feature of the severe form of the disorder is recurrent painful bleeding into the joints (hemarthrosis) and into the muscles (muscle hematomas). Joint bleeding usually involves the large joints (knees, ankles, ellbows), and the accumulation of blood in the joint space leads to severe pain. If left untreated, the recurrence of the bleeding episodes will lead to progressive deformity and crippling in severely affected patients. Soft tissue and intramuscular bleeding may lead to considerable blood loss, particularly in the retroperitoneum and the thigh. Repeated subperiostal hemorrhage with bone destruction, new bone formation, and expansion of the bone may result in large pseudotumors. Bleeding in the pharyngeal area may be life-threatening because of potential airway obstruction. Minor head traumas may cause serious CNS bleeding leading to death or permanent disability. The severity of the bleeding manifestations depends on the remaining activity of factors VIII or IX measured in clotting assays .

LABORATORY DIAGNOSIS

The laboratory diagnosis of the hemophilias is straightforward, as often the family history and the clinical manifestations suggest the diagnosis. Of the screening tests, only the activated partial thromboplastin time (aPTT) is prolonged. With the severe form of hemophilia, a prolongation in the range of 90–100 s can be expected. Subsequent testing with a specific, factor VIII- or IX-deficient plasma can prove the suspected diagnosis of hemophilia A or B. The bleeding time, the prothrombin time, and also the VWF activity should be normal.

TREATMENT

Acute bleeding episodes are treated with concentrates of clotting factor VIII in hemophilia A and clotting factor IX in hemophilia B. The plasma concentrates are derived from the plasma donations of 10,000 or more individuals. Since the mid-1980s, all commercial concentrates have been subjected to virucidal techniques to eliminate the transmission of pathogenic blood borne viruses. Since the mid-1990s, recombinant factor VIII concentrates have also been included in the treatment regimens, mainly for previously untreated persons . Spontaneous bleeding (joints, muscles) is usually controlled if the patient's factor level is raised to 20% of the normal level. If the hemorrhage is occurring at critical sites (CNS, nasopharyngeal area), before major surgery, or after serious posttraumatic bleeding, the factor VIII or IX level should be elevated to 100% and then maintained above 50% until healing has occurred.

Correlation of Factor VIII or IX Activity and Disease Severity

Coagulation factor activity (%)		Clinical manifestations
<1	Severe disease	Recurrent spontaneous bleeding episodes Joint deformities and crippling, if insufficiently treated
1–5	Moderate disease	Occasional spontaneous bleeding Postsurgical or posttraumatic bleeding
5–35	Mild disease	Postsurgical or posttraumatic bleeding

The amount of clotting factor needed can be calculated as follows:
1 unit of factor VIII/kg will raise the blood level by 2%
1 unit of factor IX/kg will raise the blood level by 1%
DDAVP provides an alternative treatment for increasing the factor VIII levels in patients with a mild form of hemophilia A. Local supportive measures in treating hemarthrosis and hematomas include resting the affected extremity and administration of systemic nonspecific drugs such as antifibrinolytic agents (e.g., tranexamic acid), which may be helpful in prevention or treatment of mucocutanous hemorrhage and after dental procedures.

Von Willebrand Disease

VWD is characterized by an abnormal platelet adhesion with or without a low factor VIII activity. VWF promotes platelet adhesion and is also the carrier for factor VIII, protecting the latter from premature destruction. This explains the combination of defective platelet adhesion and reduced levels of factor VIII. VWD is a bleeding disorder inherited in an autosomal dominant disorder.

PREVALENCE AND CLINICAL PRESENTATION

VWD is clearly the most common genetic bleeding disorder to be encountered in clinical practice, although its estimated incidence varies widely from 0.1% to as high as 1% of the general population. The most common variant, type 1 VWD, characterized by a moderate quantitative deficiency of functionally normal VWF, accounts for about 70% of patients. The most common clinical features in VWD are mucocutanous episodes, including epistaxis, easy bruising, hematomas, and menorrhagia. Postoperative bleeding occurs after tooth extraction, tonsillectomy, and, naturally, following major operative procedures. Bleeding is quite variable in each patient and within the same family, and menstrual blood loss in females varies widely

in the same family. An unexplained observation is the tendency of clinical symptoms to decrease after the patient enters the second decade of life.

LABORATORY DIAGNOSIS

Initial diagnostic tests should include the bleeding time, a factor VIII assay, and measurement of the levels of VWF. Bleeding time varies from abnormal in moderately and severely affected patients to normal in patients with mild forms of VWD. Bleeding time correlates well with the clinical symptoms.

TREATMENT

Most patients with moderate disease (usually type 1) and mild bleeding symptoms or bleeding after minor surgery will respond to DDAVP (deamino-8-D arginine-vasopresssin, desmopressin, Stimate®), a synthetic analog of the natural hormone vasopressin, which releases factor VIII, VWF, and plasminogen activator from storage sites. It is given in a dosage of 0.3 microg/kg i.v. over 30 min. DDAVP probably releases the very large VWF multimers from the endothelial cells or platelets and thus corrects the prolonged bleeding time. The effect extends over several hours, the response decreases if treatment is repeated over a period of several days. It is helpful to determine the response to DDAVP at diagnosis or before an elective procedure. Fibrinolytic inhibitors (tranexamic acid) have proved useful in reducing bleeding from the mouth, nose, or uterus